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Clinical Profile of Idiopathic Focal Segmental Glomerulosclerosis

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Abstract

Background: The cause of idiopathic focal segmental glomerulosclerosis is usually not known. Most of the patients present with primary type. The main clinical feature of FSGS is nephrotic syndrome. It causes about 10 to 15% of cases of nephrotic syndrome. Its increased incidence and high rate of progression to end stage renal disease makes it us an important disease for present study. *Method:* Thirty five patients of biopsy proven idiopathic FSGN with biochemical and hisptopathological data have been included in this study. All patients were treated on outpatient/inpatient basis. All patients were subjected to detailed general and systemic examination. Patients who had a minimum follow up of 3 months were included in the study. *Result:* Males are affected more frequently than females. Males were 26 (74%) and females were 9 (26%). The most common presentation was nephritic syndrome in 27 (77%), and clinical feature was proteinuria, in all the patients, hypertension in 16 patients (46%), and hematuria in 16 patients (46%). 16 patients (46%) progressed to renal failure over a period of 1 to 6 years. *Conclusion:* Nephrotic range (Nephritic) Proteinuria is the main clinical feature. Response to steroids is variable and unpredictable. Prognosis is better in steroid responsive as compared to non – responsive patients.

Keywords: Idiopathic Focal Segmental Glomerulosclerosis; Nephritic; Proteinuria; Renal Failure.

Introduction

Idiopathic focal segmental glomerulosclerosis is a kidney disorder presenting with nephritic range proteinuria in two thirds, and non nephritic range proteinuria in another one third of patients. The pathognomic morphology lesion in Primary FSGS is sclerosis with hyalinosis involving portions of fewer than 50% (focal) of glomeruli on tissue section [1].

The cause of idiopathic focal segmental glomerulosclerosis is usually not known. Most of the patients present with primary type. A minority of cases which are secondary, result from various causes, like reflux nephropathy, HIV, analgesics, diabetes mellitus, obesity, sickle cell disease among others. It appears that more than 50% of the nephrons must be affected for development of secondary FSGS.

The clinical course of primary FSGS varies and there is a considerable controversy as to which factors are of importance in determining prognosis or response to theraphy [2].

The main clinical feature of FSGS is nephrotic syndrome. It causes about 10 to 15% of cases of nephrotic syndrome. It usually presents with symptomatic or asymptomatic proteinuria, in association with hypertension, renal insufficiently, hematuria and abnormal urinary sediment, Proteinuria is non selective. Most cases progress to chronic renal failure, the rate of progression eo end stage renal disease being 40 to 60% over 10 years [3].

The diagnostic test is Renal Biopsy. Urine analysis proteins and cholesterol estimation, renal function tests also help in diagnosis. The goal of treatment is to control symptoms associated with nephritic syndrome and decrease urinary protein

loss. Corticosteroids and diuretics are generally prescribed, along with immunosuppressive agents, whenever needed, but the response is inconsistent.

Its increased incidence and high rate of progression to end stage renal disease makes it an important disease for study. Hence, we planned to undertake the present study to assess the clinical profile of Idiopathic Focal Segmental Glomerulosclerosis.

Objectives

To study the clinical profile of Idiopathic Focal Segmental Glomerulosclerosis.

Material and Methods

Thirty five patients of biopsy proven idiopathic FSGN with biochemical and hisptopathological data have been included in this study. All patients were treated on outpatient/inpatient basis. There were prospective and 15 retrospective cases included in the study.

Definition

Nephrotic syndrome is defined as, A clinical complex characterized by a number of renal and extrarenal features, the most prominent of which are proteinuria of more than 3.5 gms per 1.73 msq per 24 hours, hypoproteinnemia, edema, hyperlipidemia, lipiduria and hypercoagulability, in the absence of renal failure [1].

Selection Criteria

Inclusion criteria

All patients proven on biopsy to be having FSGS were selected for the study. Also other presenting features like edema (localized or generalized), foamy urine, hematuria were helpful in diagmosing the patients selected for the study.

Exclusion criteria

All patients with diabetes mellitus malignant hypertention, amyloidosis, pregnancy, systemic lupus erythematosis, drug reaction, glomerulopnephritis, reflux nephropathy, and congenital disorders were excluded from the study.

All patients were subjected to detailed general and systemic examination.

Patients who had a minimum follow up of 3 months were included in the study.

All patients were investigated as follows –

1) Urinary Indices –

a) Routine and Microscopic examination were done.

b) Quantitative test for urinary proteins – Sulfosalicylic acid test

c) Estimation of 24 hour urine protein by ESBACHES qualitative test.

d) Spot test for urine equivalent to 24 hours urinary proteins by estimation of urinary albumin / creatinine ratio > 0.25 mg / dl.

2) Biochemistry-

a) Serum proteins – (normal 5.5 to 8 g / dl)

Serum albumin – (normal 3.5 to 5.5 g /dl)

Serum globulin – normal 2 to 3.5 g / dl)

b) Serum Urea – GLDH / Kinetic method (normal 15 to 45 mg / dl)

c) Serum Creatnine – Alkaline Picrate method (normal 0.5 to 1.5 mg/ dl)

d) Fasting lipid profile

e) Serum electrolytes

f) Blood Sugar – (Fasting and Post – prandial plasma true glucose m levels in mg/dl)

3) Radiology –

a) Ultrasonography – Done to calculate kidney size and to perform

USG guided biopsy.

4) Kidney Biopsy –

Kidney biopsy was done in all 35 cases using a Trucut Needle. The tissue was preserved in 10% neutral buffered Formalin and embedded in a Paraffin block. Later on 4 micron thick sections were taken, deparaffinised and stained with hematoxylin and eosin. Other stains used as and when needed are PAS for staining sclerotic tissue and SILVER stain for staining hyalinosis. The tissue mounted slides were studied by Pathologists and reviewed by us.

5) Histological Criteria –

Morphology under Light Microscopy showing Focal and Segmental Sclerosis and enlargement of the unscarred glomeruli.

Statistical Analysis

Descriptive statistics such as mean, SD and percentage were used to present the data. Relationship between variables was assessed by using Chi-square test or Fisher's exact test. A p-value less than 0.05 were considered as significant.

Result

Of the total 35 patients 74% were between 11 to 40 age group. There were 26 males and 9 females. Incidence of males was 74%, and females were 26%.

Table 1: Serum Albumin Levels

Serum Albumin Levels (mg /dl)	No of Patients	Percentage of Total (%)
0 to 1	0	0
1.1 to 2	12	34
2.1 to 3	17	49
3.1 to 4	6	17
4.1 to 5	0	0

Majority of patient had serum albumin levels in the range of 2 to 3 mg / dl (49%) followed by 1 to 2 mg / dl (34%), 3 to 4 mg / dl (17%) (Table 1).

Table 2: Range of Proteinuria and Progression to CRF

-Proteinuria gm / d	Normal Renal Functions	Patients With CRF	Percentage of Total (%)
Nephrotic (Nephritic) Range (>3.5)	27	15	55
Non Nephrotic Range (<3.5)	8	1	12

Out of 35 patients, 27 (77%) had nephritic range proteinuria, of which 15 (55%) had CRF. 8 patients (23%) had non nephritic range proteinuria, of which only 1 (12%) had CRF. Progression to ESRD was proportional to the amount of proteins list in the urine (Table 2).

Table 3: Relationship Between Steroid Therapy and ESED

Response to Steroids	Normal Renal Functions	End – Stage Renal Disease	Total No. of Patients
Responded	16 (62%)	10 (38%)	26 (100%)
No Response	3 (33%)	6 (67%)	9 (100%)

χ^2-value = 1.16 p-value=0.28

26 patients responded to steroids and 10 (38%) had ESRD whereas 6 patients (67%) of the non responders had ESRD (Table 3).

Table 4: Response to Steroid & Relapse Rate after Steroids

Response to Steroid	No. of Patients Response to Steroid	Relapse	Percentage (%) of Total
Complete	10	3	30
Partial	16	7	44
Resistant 1	9	0	0
Total	35	10	38

Of the total 35 patients treated with steroids 26 (74%) responded. In 10 (28%) patients who had a complete response 3 (30%) had a relapse. In 16 (46%) patients who had a partial response to steroids 7 (44%) had a relapse. Of total patients who responded to steroids 10 (28%) had relapse (Table 4).

Serum Creatinine Values at Last Follow Up -

All patients had normal serum creatinine values at the first clinical presentation. At the last follow up 19 (54%) patients of the total continued to have normal renal functions (serum creatinine <1.5 mg / dl). The other 16 (46%) had developed renal failure, which was defined as serum creatinine values >1.5 mg /dl.

Table 5: Follow Up in Years and Progression to ESRD

No. of Years	No. of F / U Patients	No. of Patients With ESRD	Percentage (%)
3 months to 1 year	3	0	0
1.1 to 2 years	5	2	28
2.1 to 3 years	6	2	33
3.1 to 4 years	7	3	43
4.1 to 5 years	6	4	66
>5 years	8	5	63

Out of 35 patients followed up, 16 patients (46%) had developed end stage renal failure after 5 years.

Four (4) patients (28%) of 14 had ESRD within 3 years of onset of FSGS. Most of the patients (57%) had ESRD between 3 to 6 years of disease (Table 5).

Table 6: Significance of Hematuria.

No. of Patients	No. of Hematuria	With Hematuria	Total
No. Renal Failure	13 (68%)	6 (32%)	19 (100%)
With Renal Failure	6 (38%)	10 (62%)	16 (100%)

χ^2-value = 2.22 p-value=0.14.

With normal renal functions, 13 (68%) patients had no hematuria, and 6 (32%) had hematuria. With renal failure, 10 (62%) patients had hematuria, and 6 (38%) did not have hematuria (Table 6).

Treatment with Cyclophosphamide –

Three patients were treated with cyclophosphamide. They had frequent relapse with steroids. The dose was 5 mg / kg body weight given in pulse dose every month for six months along with alternate day steroids. All three patients had remission initially but further progression to ESRD occurred in one and one died of non renal complications.

Discussion

Incidence of Age and Sex –

In our study there were 26 male and 9 female patients. Male to female ratio was 3:1. Patients in this study were in the range of 2 to 60 years. About 65% of patients were in the range of 15 to 40 years of age. The mean age of onset was 21 years. Incidence for male patients was 74% and 26% for females. The mean age of onset for males was 20.8 years and for females was 21.5 years.

Adhikari showed the increased incidence of FSGS in children in India from 1.8 to 20% over the last 30 years. Our studies showed similar results. Incidence was 17% (6) in the children age group [4].

Our study concurred with Camerons study, where the mean age of onset was 21 years and 60% of patients presented in age group between 15 to 40 years [5].

Significant male preponderance has been reported in the studies of Newmann [6] and Beaufils [7].

Other studies having a male predominance were those of Morita M. [8] with 55% of patients being male, Rydel JJ, [9] where 58% of his study group had male patients, and Rennert WP [10] having 60% males in his study.

Compared to above studies the male/female ratio was higher in our studies. The age group and mean age of onset are similar to the reference studies.

Clinical Features –

Serum Proteins And Proteinuria –

The mean serum proteins in our patients at presentation was 4.61 gm/dl, with a range of 3 to 5.9 gm/dl. The mean serum albumin was 2.31 gm / dl, with a range of 1.1 to 3.6 gm / dl. Our patients showed lower levels of total proteins and serum albumin. Twenty four hours urinary protein excretion in our patients ranged from 1.5 to 7.6 gm / day with a mean of 4.77 gm/day.

In a study of 183 patients at the George Town University Hospital, 18 they found that severity of proteinuria does not have exact correlation to serum protein concentration. In our study the serum protein values were found to be on the lower side. This could also reflect the initial poor nutrition of the cases under study.

In the present study 27 (77%) patients had nephritic range proteinuria, of which 15 (55%) developed ESRD within 4 to 7 years duration. 8 (23%) patients had non nephritic range proteinuria of which only 1 (12%) developed ESRD. Of total 16 (46%) patients had ESRD.

The findings of the present study coincides with the study of Beaufils et al. [7] who reported that persistent proteinuria was associated with a 10 year survival of only 45%. He also proposed that persisting non nephritic proteinuria had 10 year survival of more than 90%.

Similarly Cameron et al. [5] in his study stated that patients with initial symptoms of nephritic syndrome showed a 10 year survival of only 30%, whereas those patients with asymptomatic proteinuria had a 10 year survival of 90%.

Korbet SM, in his study stated that 50% of patients with nephritic range protgeinuria progressed to ESRD in 3 to 8 years duration as compared to 80% survival over 10 years in patients having non nephritic proteinuria [11].

Velosa JA in his study proposed that renal survival from biopsy to end stage was 7 years in patients with nephritic range progteinuria and 3 years in patients with massive proteinuria [12].

Rydel JJ [9] proposed renal survival of 45% at 6 years in patients with nephritic range proteinuria and 90% with nonnephrotic range proteinuria.

Higher degree of proteinuria and lower serum albumin levels are associated with severe disease. The severity and duration of proeteinuria affects the course of the disease. Higher protein losses is an important predictor of progression to ESRD, as stated by Korbet SM et al. [11].

Hematuria

Hematuria is a frequent finding in FSGS. In our study 16 patients had hematuria as a clinical feature. Of the total 16 (46%) patients who had hematuria, 6 (32%) patients maintained their normal renal functions, and 10 (68%) patients developed renal failure. Most of them had microscope and painless hematuria.

Beaufils et al. [7] and Cameron [3,13] in their studies mentioned that hematuria is a frequent clinical finding in patients with FSGS. They found that about 25% to 70% of patients with FSGS have hematuria along the course of the disease.

Korbet S M, in his study stated that 32% patients had hematuria [11].

Tsau Y K et al. in their study found 39% of patients having hematuria [14].

Findings of our study have values similar to those given in above studies.

Patients with renal disease hematuria are not significant in those patients who develop ESRD as compared to those who have normal renal functions. Our study had a small number of patients and further studies are needed to be followed up to determine the significance of hematuria.

Renal Functions

Serum creatinine is most important biochemical predictor of renal function. Renal failure was defined as serum creatinine levels above 1.5 mg/dl. All the patients included in our study had normal renal functions at the beginning of the study. At the end of the study 19 (54%) patients retained their normal renal functions (serum creatinine <1.5 mg/dl) and 16 (46%) patients had developed renal failure (serum creatinine > 1.5 mg/dl at the end of 5 years. Among patients who developed renal failure 12 (75%) reached end stage between 3 to 6 years. There was male predominance (M/F ratio was 4:1). Most of the patients were between the age groups 11 to 40 years in which the disease is more prevalent.

Cameron et al. [3,5] used actuarial survival curves to establish that between 40 to 60% patients had renal failure in 5 to 10 years.

Beaufils et al. found that upto 55% of patients have renal failure in 5 to 10 years [7].

Korbet S M in his study found that 50% of his patients having serum creatinine >1.3 mg/dl at the onset and severe proteinuria had end stage disease in 3 to 8 years [11].

In yet another study reported by Mongeau et al., the survival rate for FSGS was 56% after a 20 year follow up period [15].

Rydel JJ reported that renal survival was 40% at the end of 5 years in adult patients having severe non responsive nephritic syndrome [9].

Velosa et al. in his study stated that high serum creatinine values and interstitial fibrosis at diagnosis have a poor prognosis [12].

Similarly Alexopoulos et al. [16] mentioned in their studies that serum creatinine and response to steroids are the most important prognostic markers. In their study patient responding to treatment had stable renal functions whereas, in those who did not respond to treatment more than 50% had doubled their serum creatinine values and developed ESRD.

Korbet SM proposed that serum creatinine levels above 1.3 mg/dl at onset were consistently a significant positive predictor of progression to ESRD [11].

Progression to renal failure depends upon a number of factors, like age of onset as proposed by Gulati et al. [17] He mentioned that early age of onset (<16 years) was associated with better response to treatment and prognosis as compared to patients who have late onset (>16 years) FSGS. In the present study of the 14 children only 5 (35%) had renal failure compared to 11 of 21 (52%) in adults. However, statistically p value >0.5 and is not significant.

Duration of disease is an important prognostic factor. In the present study 4 (28%) of 14 patients with disease less than 3 years had ESRD whereas 12 (57%) of 21 patients with disease more than 3 years had ESRD. Statistically p value > 0.5 and is not significant.

In both the above factors number of patients in the study was very less and so the findings may not be significant.

Degree of proteinuria, as stated by Beaufils [7], Cameron [3] and others, and response to steroids, as discussed below are also important predictors of renal failure.

Management

Steroids

As per the results of our study it may be stated that FSGS is a disease which is difficult to treat. All 35 patients were initially treated with steroids at a dosage of 2 mg/kg/d for initially 2 weeks after the initial response, 1 to 2 mg/kg/d was given on alternate days for a duration of 16 to 24 weeks. The dose of steroids was then reduced in a stepwise fashion during the next 4 to 12 weeks, depending upon the rate of response. 26 (74%) patients responded and 9 (26%) had no response to steroids from the onset. Of the patients who responded 10 (38%) had complete remission and 16 (46%) had partial remission. Relapse was seen in 10 (38%) patients who initially responded well to steroids. 3 (30%) of 10 patients with complete

response, and 7 (44%) of 16 patients with partial response had relapse. The rate was maximum in the 21 to 30 age group. Number of relapse also affected the outcome of the disease.

Among the 26 responders 19 (73%) had normal renal functions and 7 (27%) developed ESRD, whereas 6 (67%) of 9 patients in non responder group had ESRD. With relapse 6 (60%) patients had ESRD at the last follow up. The response to steroids in each individual is difficult to predict. As a result different studies have given variable results.

In the study performed by Alexpoulos et al. in 33 patients, 28% had complete remission, 44% had partial remission and 28% did not respond to steroid therapy [16].

In another study, Martenelli had sustained remission in 4 (10%) patients, frequent relapse in 13 (33%), and renal failure in 10 (26%) patients out of 39 [18].

Rydel et al. revealed that 15 (50%) of his 30 patients responded to steroids of which 10 (67%) had complete response and 5 (33%) had partial response. None of them had renal failure. Of the other 15 (50%) patients who did not respond to steroids, 6 (40%) developed renal failure over 5 years. Survival rate for patients not responding to steroids was 66% at 5 years and 41% at 10 years respectively [9].

Meyrier and Simon reported that in 51 patients with good initial response to steroids, 4 (13%) had renal failure compared to a study where 45 (49%) of 83 patients without initial good response to prednisone developed ESRD [19].

In Habibs study of 105 patients, among those who responded to steroids 1 (5%) of 21 progressed to ESRD and in patients who did not respond initially to steroids 35 (42%) of 84 had renal failure, 4 (11%) had partial remission and 32 (35%) had complete remission [20].

Results of our study correlate with the study of Alexopoulos et al. [16].

Response to steroids is a significant predictor of renal outcome in patients with FSGS. Statistically this is significant as p value <0.05. Patients with response to steroids have a good outcome and prolonged renal survival as compared to those who do not respond to steroids. Of the patients who respond, prolonged remission has better prognosis and patients who have frequent relapses have higher rates of renal failure.

The response to steroids was comparable to the above mentioned study, however renal failure was higher in both responders and non responders. This could be because of the fact that our study had a very short follow up period, it was random, had no controls, and also that the protocol and duration of treatment is not fixed or standardized and response is not predictable. Rydel JJ stated that prolonged course of prednisone offers hope of a remission and a highly significant change in renal outcome in a substantial number of patients [9].

Whether treatment with steroids alters the natural history of FSGS or identifies a subgroup with a better prognosis is unknown.

Cyclophosphamide

Three patients (8.5%) having frequent relapse and no response to steroids were treated with cyclophosphamide. Two had remission of which one eventually progressed to ESRD and one patient died due to non renal complications.

From the discussion it may be inferred that the prognostic factors for FSGS are age of onset, serum creatinine levels at initial follow up degree of proteinuria, response to steroids, and duration of disease.

Biopsy findings – Hilar and tip lesions, interstitial fibrosis and mesangial hypercellularity have been reported to correlate with poor prognosis. But as the patients presented in various overlap histologically, at the onset of disease it was not possible to prognosticate them.

Most of our findings were concurrent with the Reference studies. Focal sclerosis is a slowly progressive disease of the kidney which leads to end stage renal failure in almost half the patients, inspite of treatment. Steroids to some extent may retard or slow the disease course when given over a time along with other modalities of treatment. But ultimate prognosis is still not very encouraging and remains bad. Our study was performed on a very small number of patients and larger studies are required to focus on various factors affecting disease course and prognosis. The rising incidence of Focal Segmental Glomerulosclerosis all over the world and its bad prognosis is a matter of major concern.

Conclusions

Idiopathic Focal Segmental Glomeruloscleros is affects individuals in adolescent and young age group. Males are affected more frequently than females. Nephrotic range Proteinuria is the main

clinical feature. Response to steroids is variable and unpredictable. Prognosis is better in steroid responsive as compared to non – responsive patients. Serum creatinine and proteinuria are the most important predictors of outcome. Approximately half the patients progress to end stage renal failure in about 5 year's duration.

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